

# **Neurobiology of Addiction**

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**Michael J. Bohn, M.D.**

**Assistant Clinical Professor of Psychiatry  
University of Wisconsin Medical School  
Medical Director, Gateway Recovery  
Consultant, WPS Insurance Company  
Consultant, Wisconsin Bureau of Substance Abuse  
Services**

# **Neurobiology of Addiction**

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**Developmental and Genetic Factors**

**Brain Structure and Reward Circuits**

**Heroin and Cocaine**

**Conditioned Craving and Relapse**

**Newer Treatments: Rx, CVR**

**Treatment Implications**

# Development of Addiction

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- AGE OF ONSET of ALCOHOL/ DRUG USE DUE TO ACCESS, SOCIAL NETS, NOT HEREDITY
- ESCALATION OF DRINKING HERITABLE
- SOME PERSONALITY TRAITS [SENSATION SEEKING, SHYNESS/DEPRESSION]  
HERITABLE RISKS
- AGE 3 BEHAVIOR: 2 PATHS-HYPER & SHY
- ALCOHOL TOLERANCE + FAMILY ALCOHOLISM EACH INCREASE RISK 3-4X;  
BOTH INCREASES RISK 8X, TO 60%



# **GENETICS OF ALCOHOL & DRUG USE IN ANIMALS**

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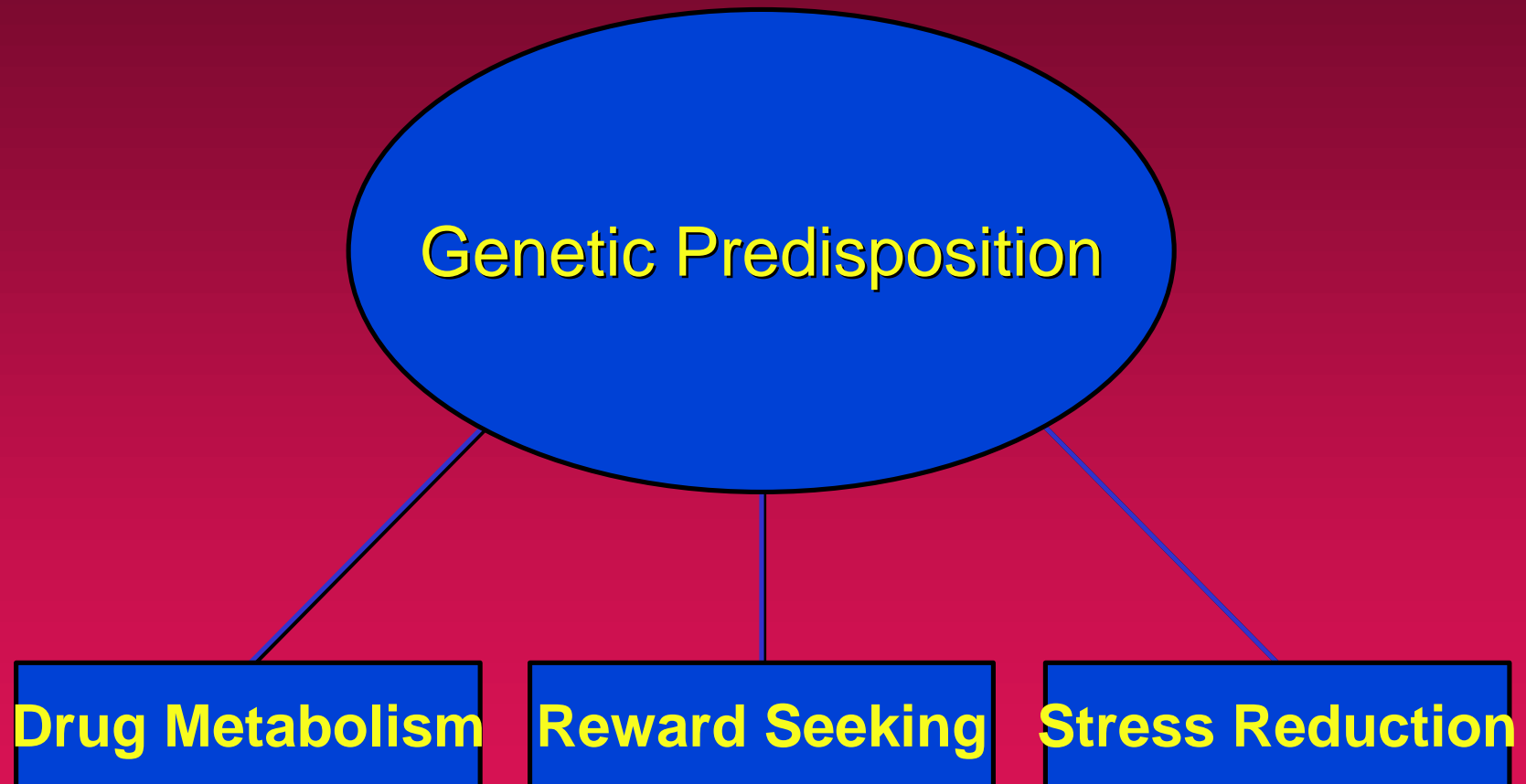
- **INBRED RATS AND MICE DIFFER IN**
  - **PREFERENCE FOR ALCOHOL AND DRUGS**
  - **TOLERANCE FOR ALCOHOL AND DRUGS**
  - **WITHDRAWAL EFFECTS**
  - **POST-STRESS RATE OF ALC/DRUG USE**
- **GENETICALLY ENGINEERED MICE DIFFER IN RESPONSE TO COCAINE MOTOR EFFECT**

# GENETICS OF ALCOHOLISM

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- **ALCOHOLISM IS FAMILIAL:**
  - **4X-INCREASED IF PARENT ALCOHOLIC**
- **IDENTICAL > FRATERNAL TWINS**
- **ADOPTION: NO EXTRA RISK**
- **ALCOHOL TOLERANCE + FAMILIAL ALCOHOLISM INCREASES RISK 8-FOLD: 60%**
- **3 RISK GENES SO FAR; 1 PROTECTIVE GENE**
- **ALCOHOLISM VERY HERITABLE: 60-65%**

# Alcohol and Drug Dependence

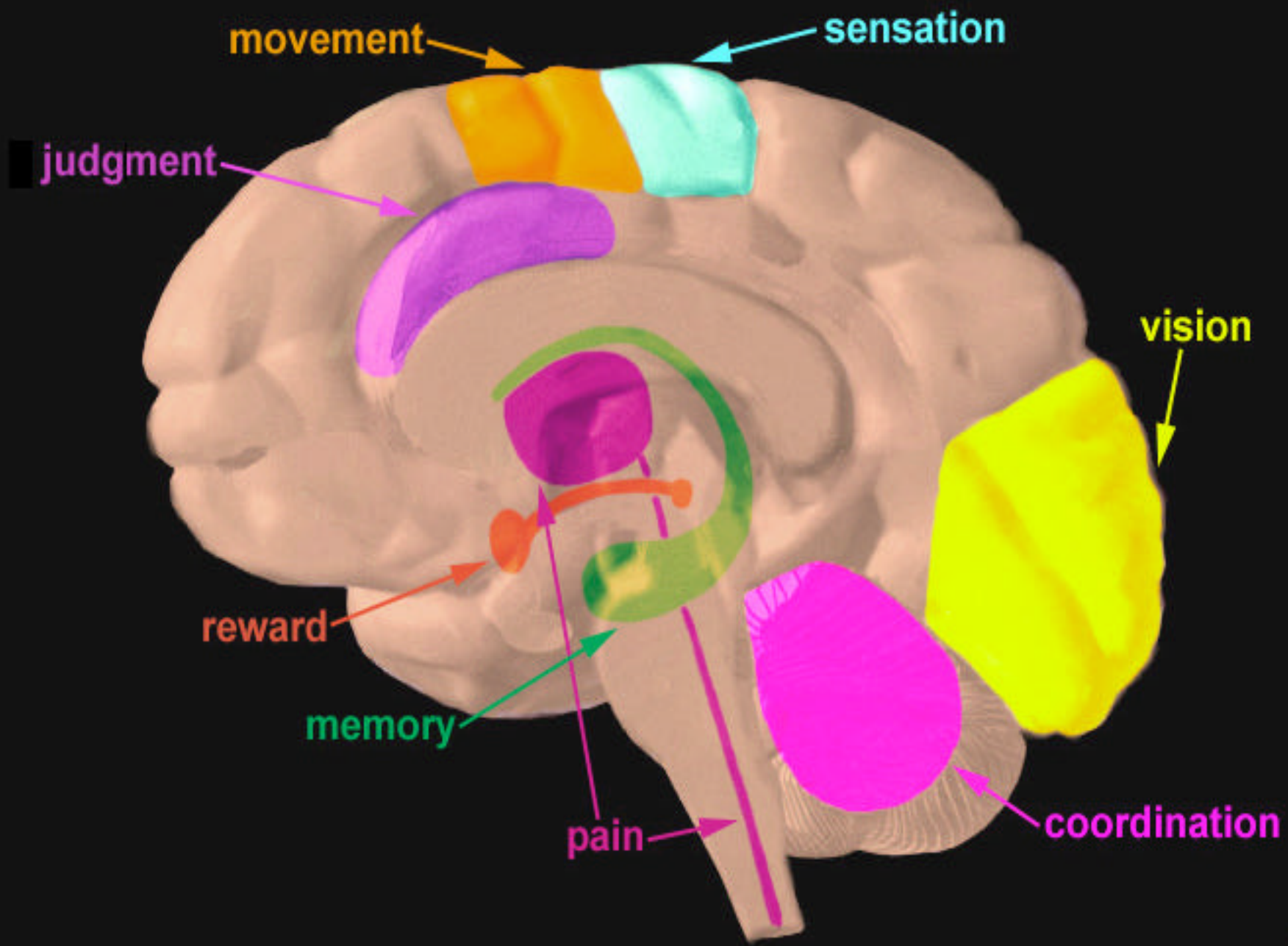


# Introduction to the brain

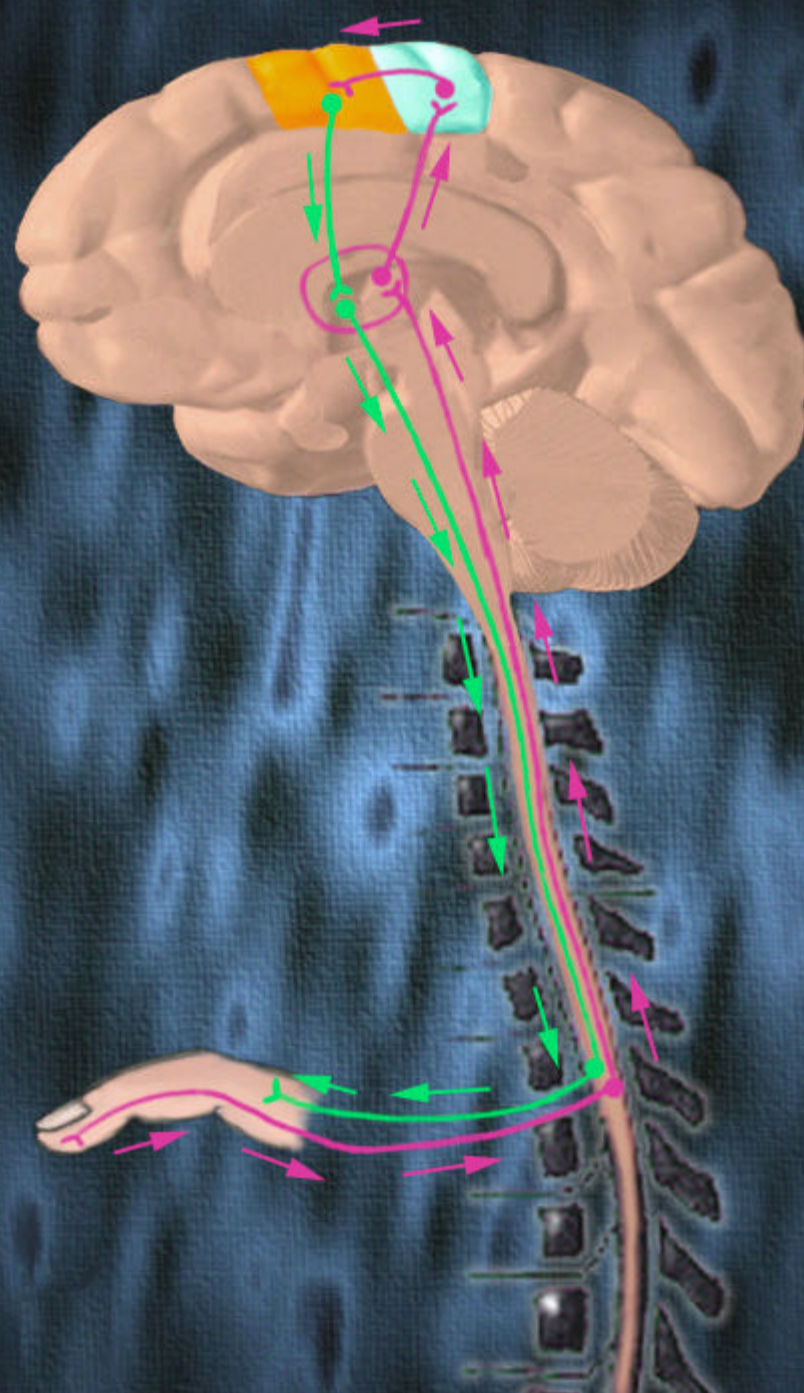


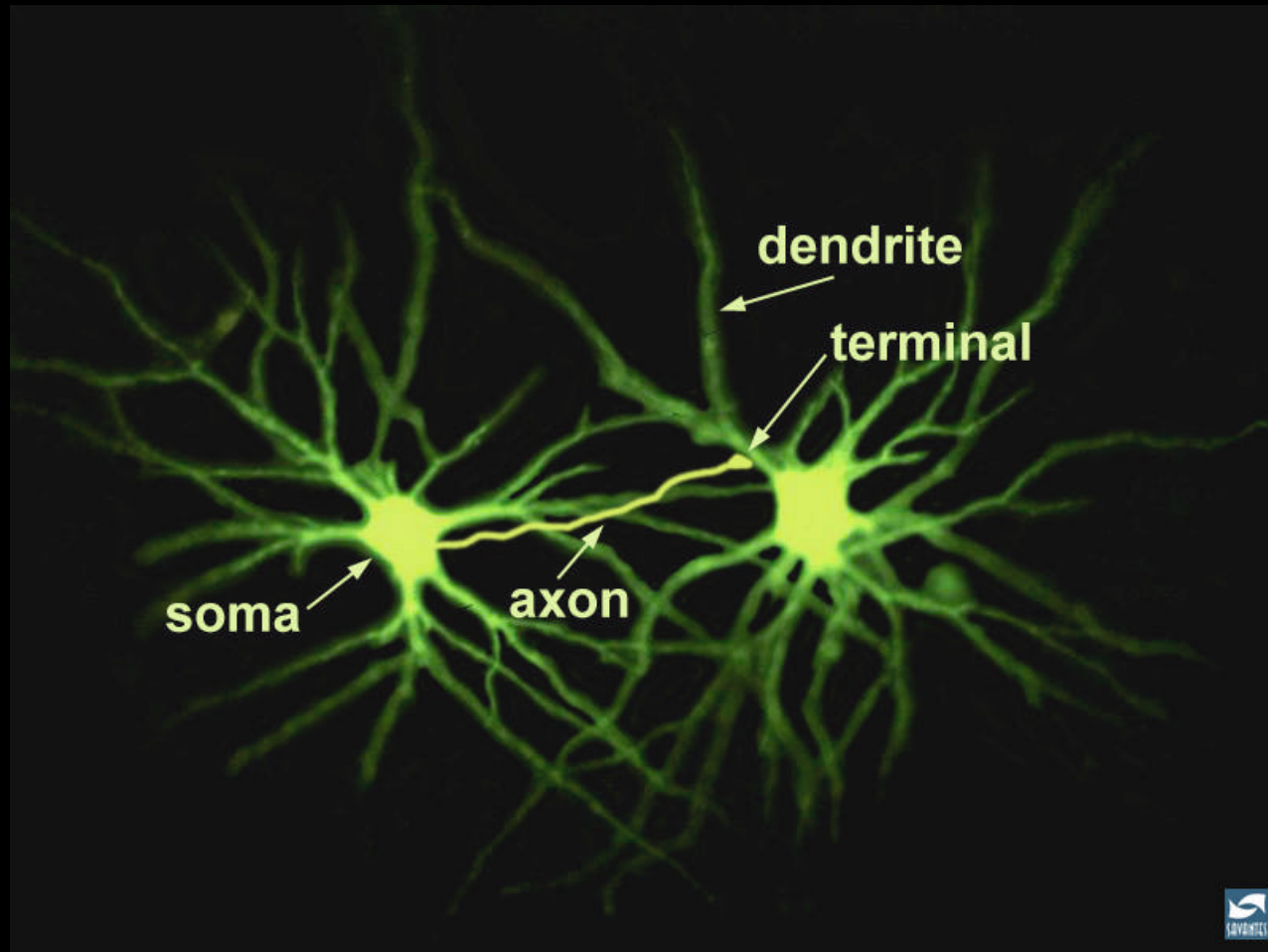


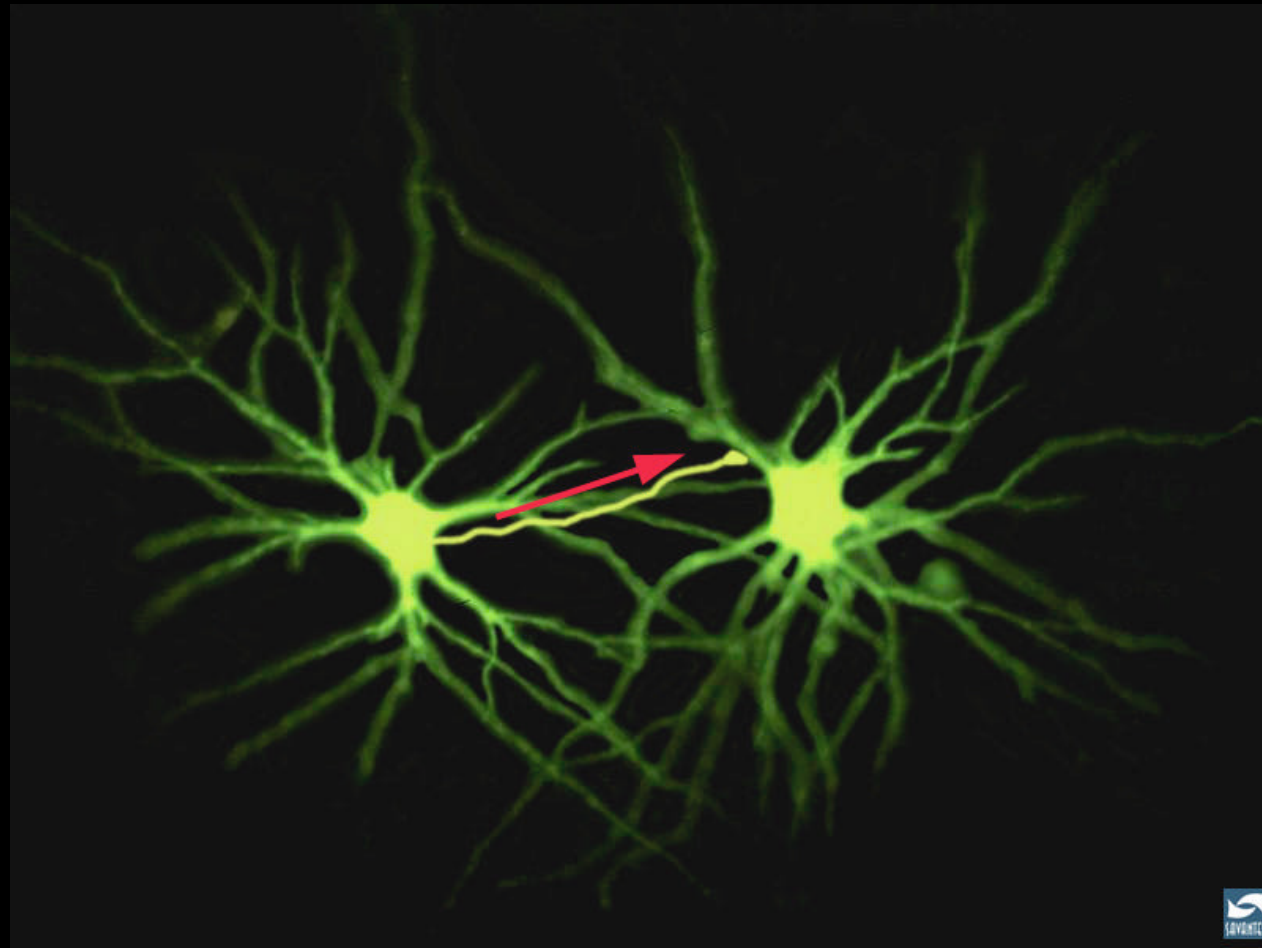


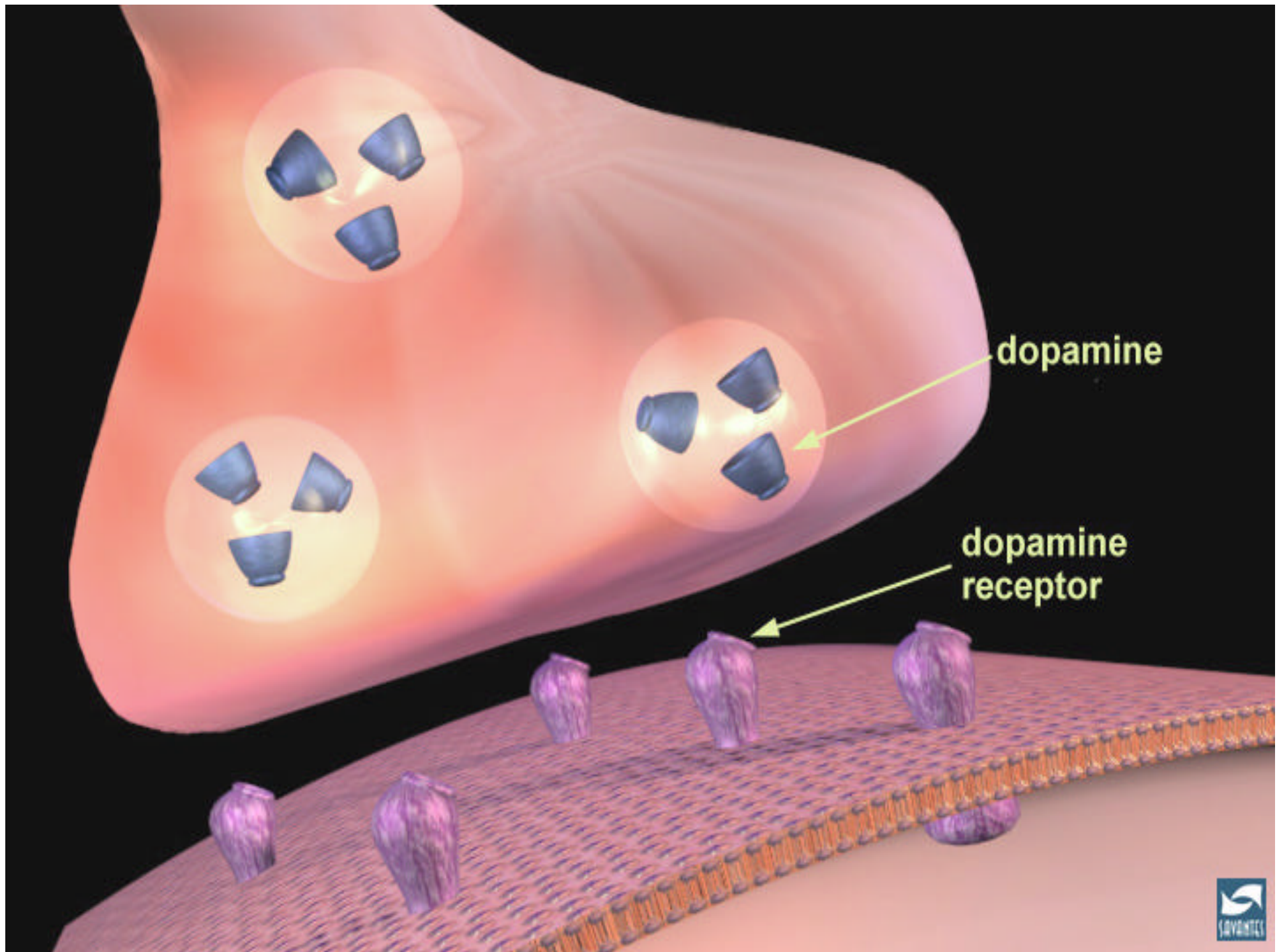




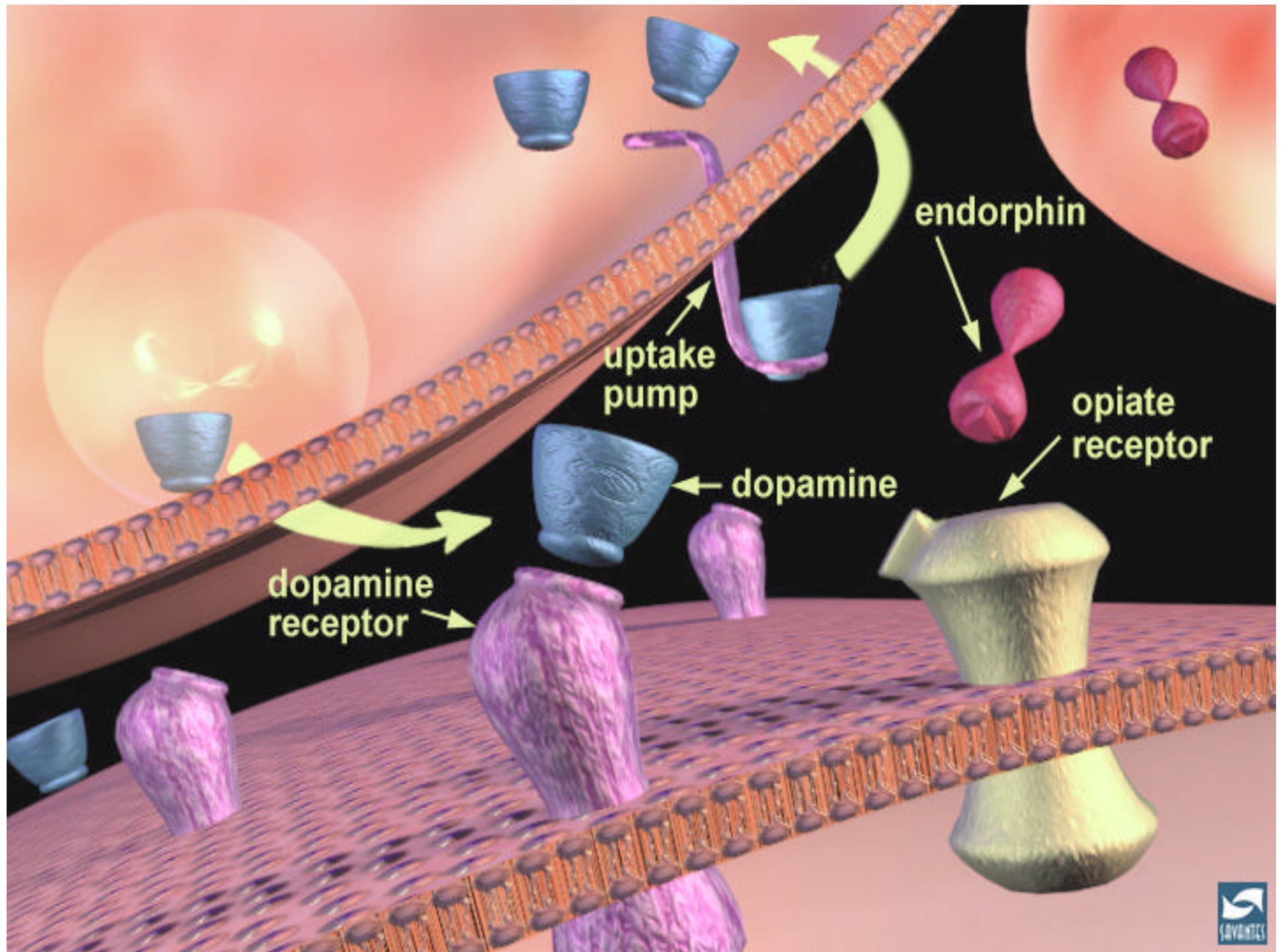












**The true worth of a man is to be measured by the objects he pursues.**

**- Marcus Aurelius**



# The Reward Pathway and Addiction



# Natural Rewards

Food  
Water  
Sex  
Nurturing

# Brain Reward System

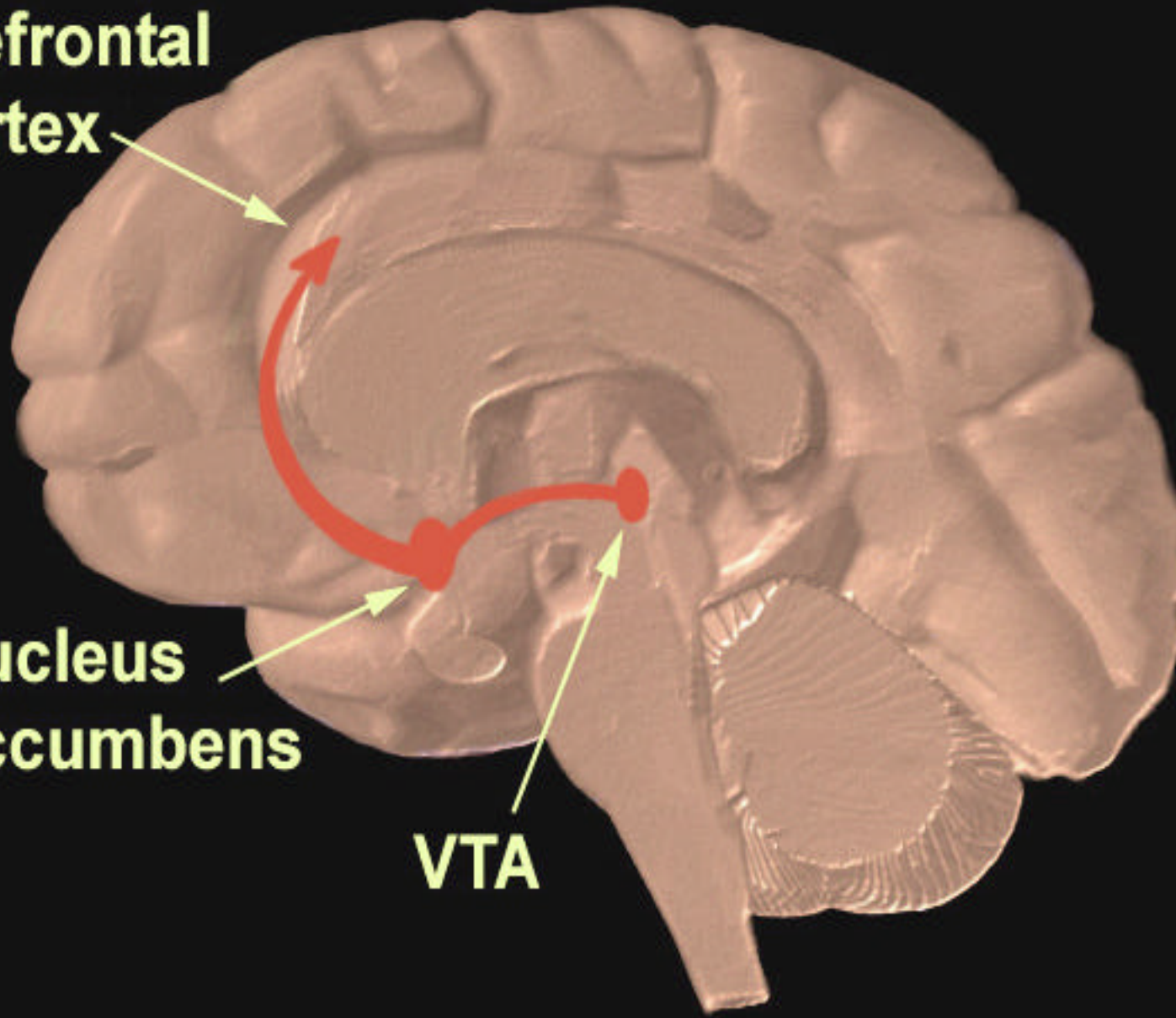
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- **DOPAMINE** TRANSMITTER CHEMICAL
- APPROACH SYSTEM; SETS PRIORITIES
- VENTRAL TEGMENTAL AREA [VTA]
- NUCLEUS ACCUMBENS [NAcc]
- CONNECTED TO BRAIN AREAS FOR  
**PLANNING** [PREFRONTAL CORTEX]  
**EMOTION** [AMYGDALA]  
**MEMORY** [HIPPOCAMPUS]

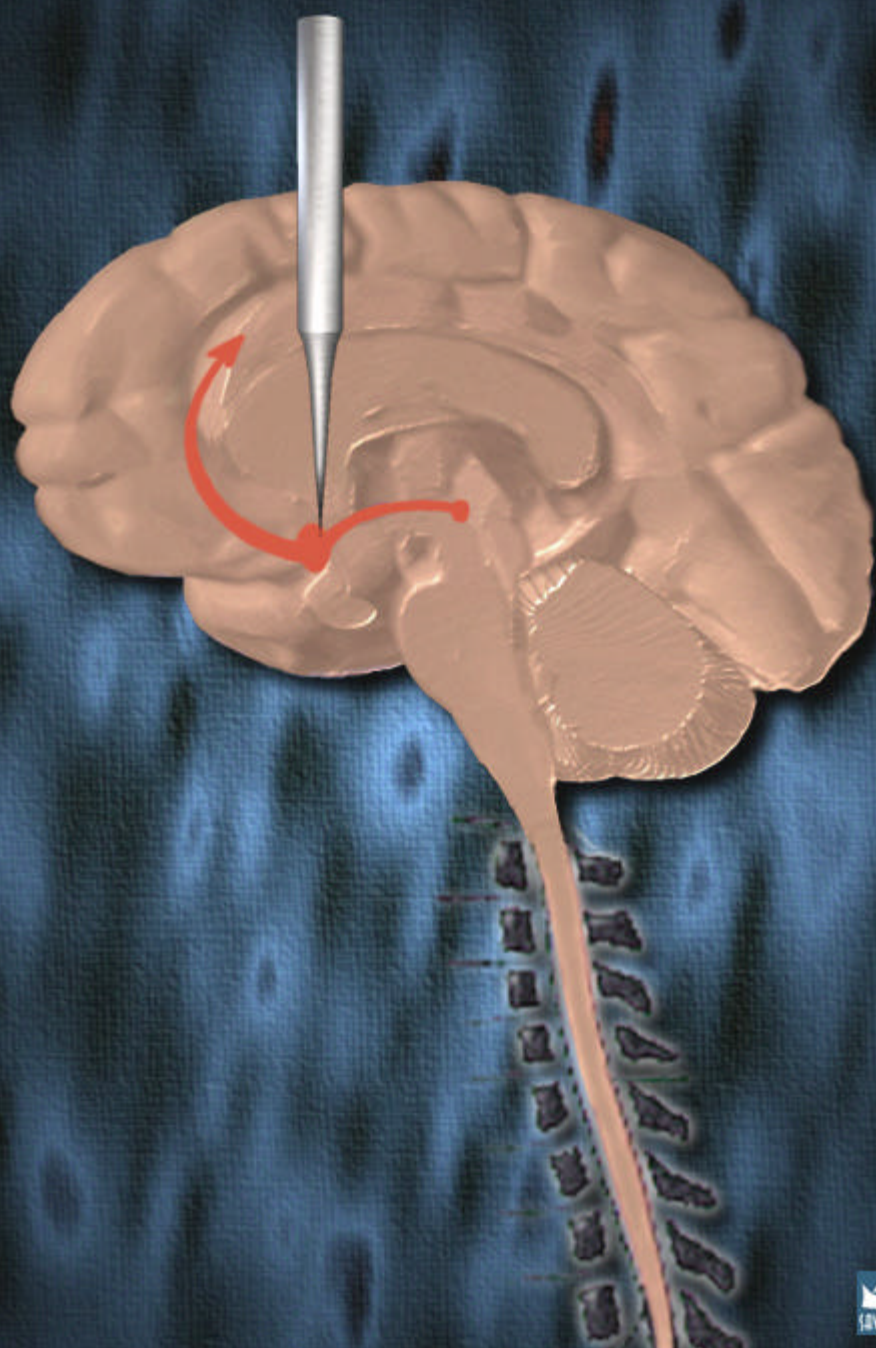
**prefrontal  
cortex**

**nucleus  
accumbens**

**VTA**







# Dopamine Release in Brain Reward System

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- ENHANCED BY ELECTRICAL STIMULATION
- INCREASED BY

PALATABLE FOOD: 50%-

SEX 50-100%-

- ONLY INCREASED BY ADDICTIVE DRUGS,  
ALL OF WHICH ARE NATURAL PLANT  
PRODUCTS

**I feel sorry for people who don't  
drink.**

**When they wake up in the morning,  
that's as good as they're going to  
feel all day.**

**Frank Sinatra**

# Addictive Substances Markedly Increase Dopamine (DA) Release

## REWARD

## Peak DA Release

PALATABLE FOOD:

50%-

SEX

50-100%-

ETHYL ALCOHOL

125-200% -

CANNABIS [THC]

125-175% -

NICOTINE

225% -

MORPHINE/HEROIN

150-300% -

COCAINE

400% -

AMPHETAMINE

1000% -

RA Wise, 2000



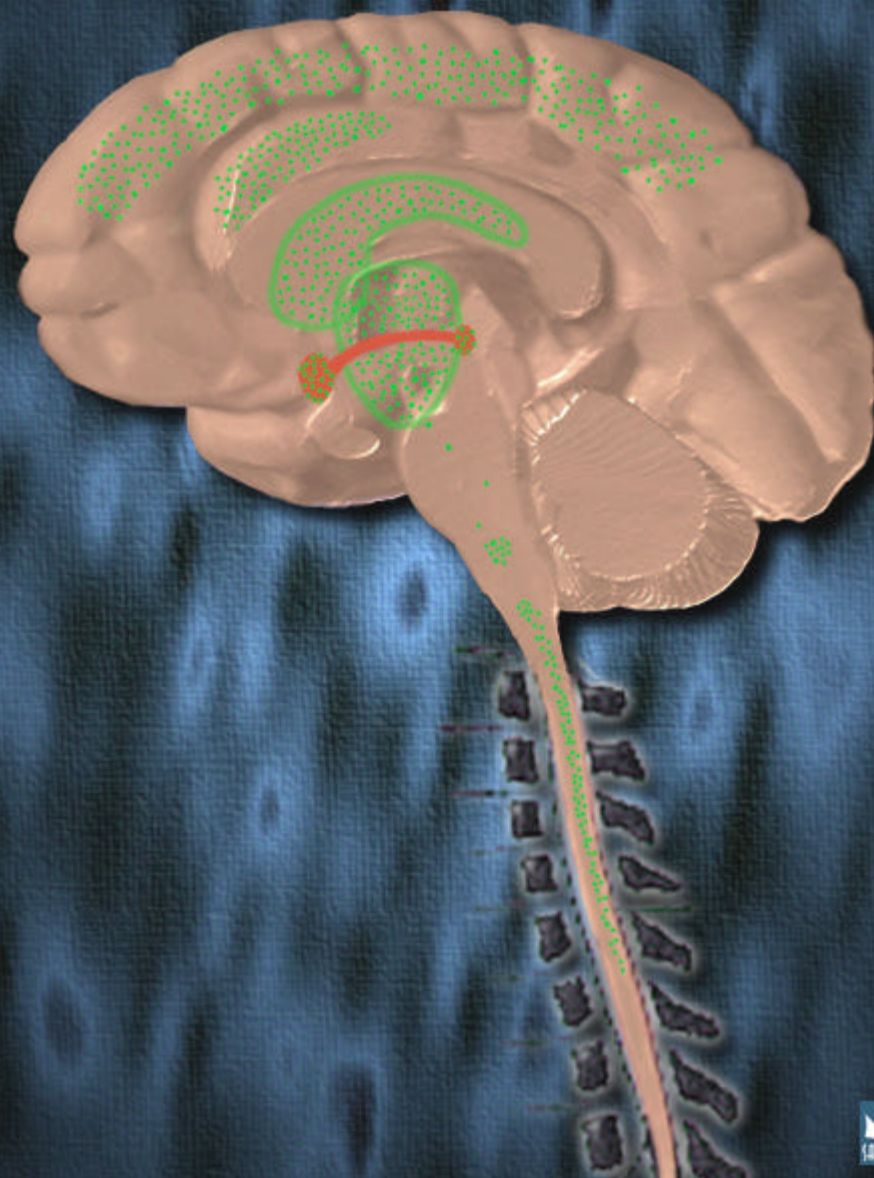
# Addiction

**A state in which an organism engages in a compulsive behavior**

- **behavior is reinforcing (rewarding or pleasurable)**
- **loss of control in limiting intake**



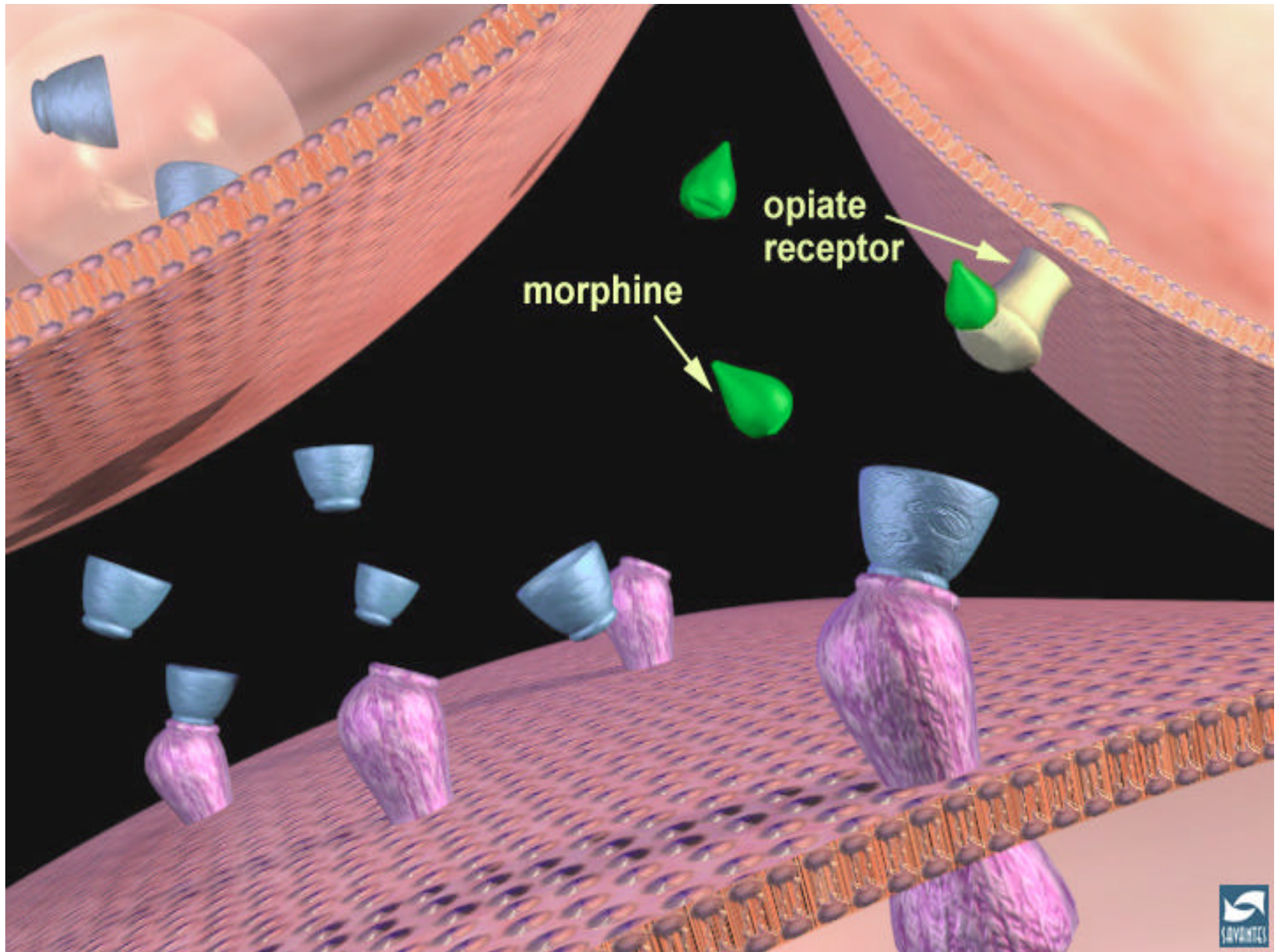
# The Action of Heroin (Morphine)



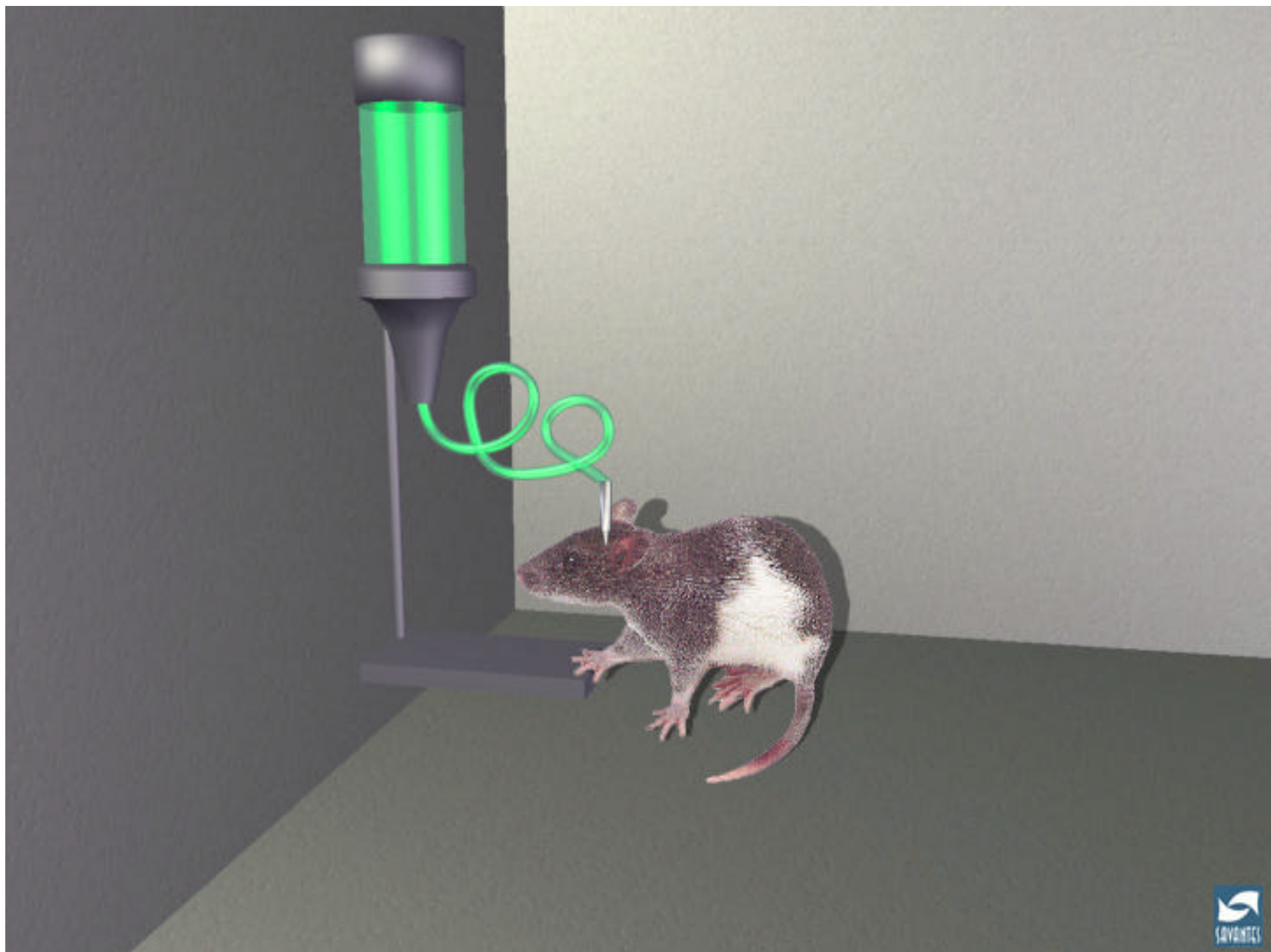


morphine

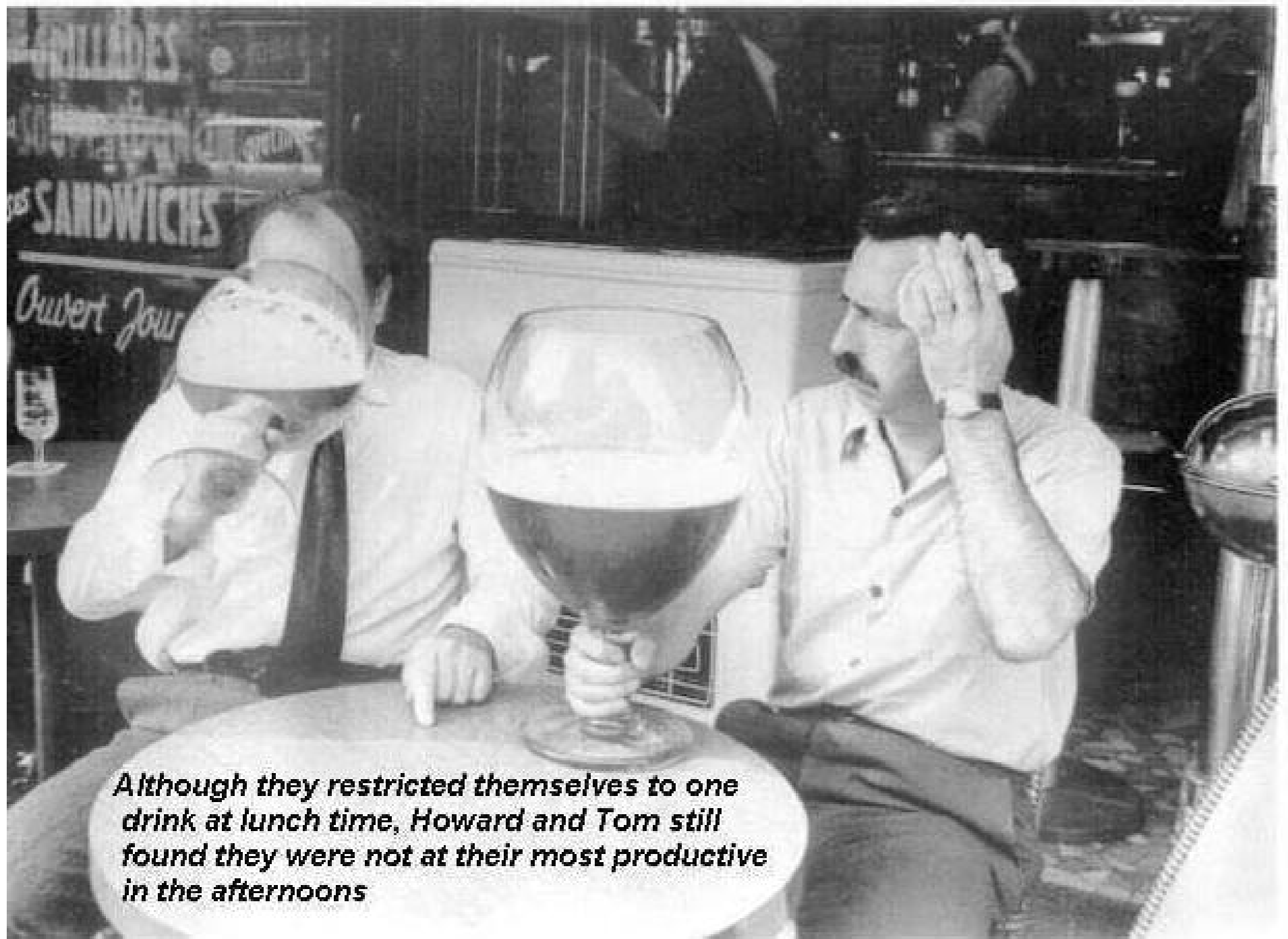
opiate  
receptor









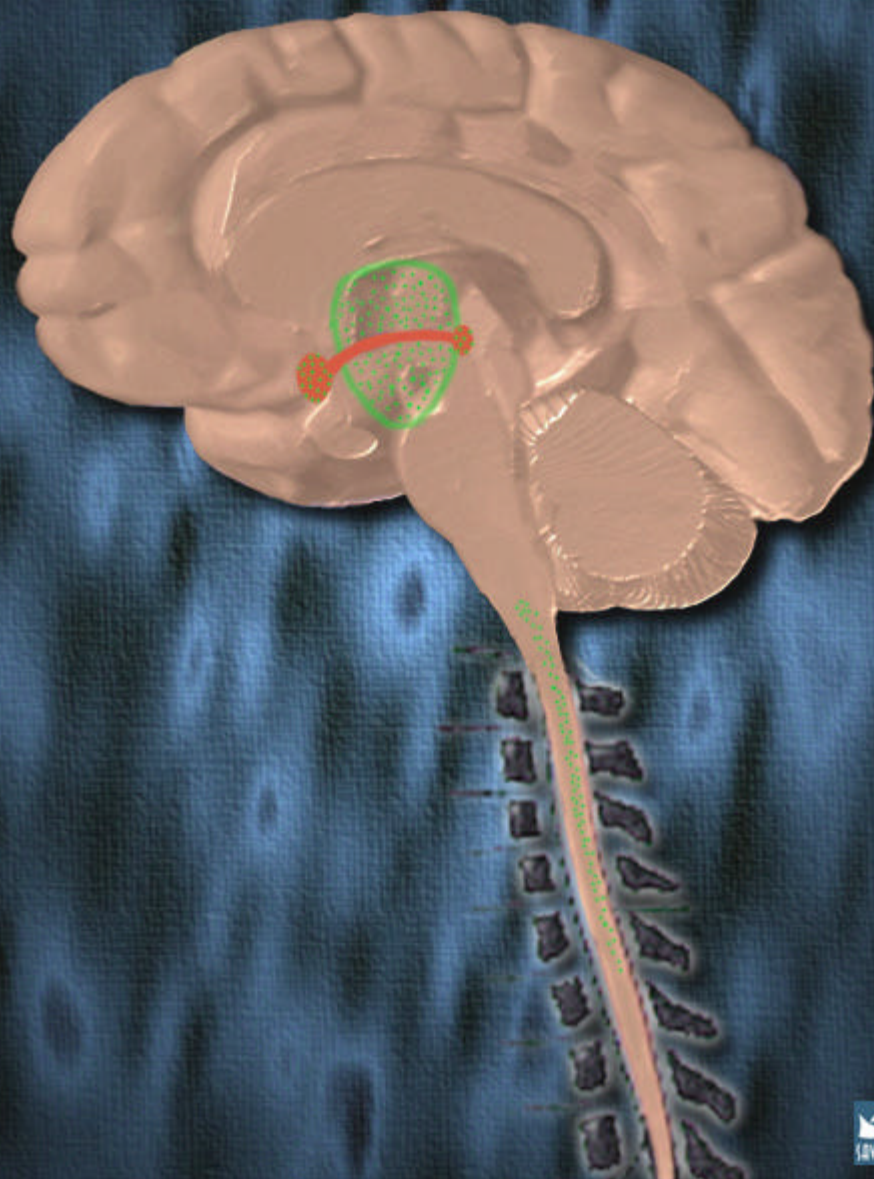


# Tolerance

A state in which an organism no longer responds to a drug

- a higher dose is required to achieve the same effect



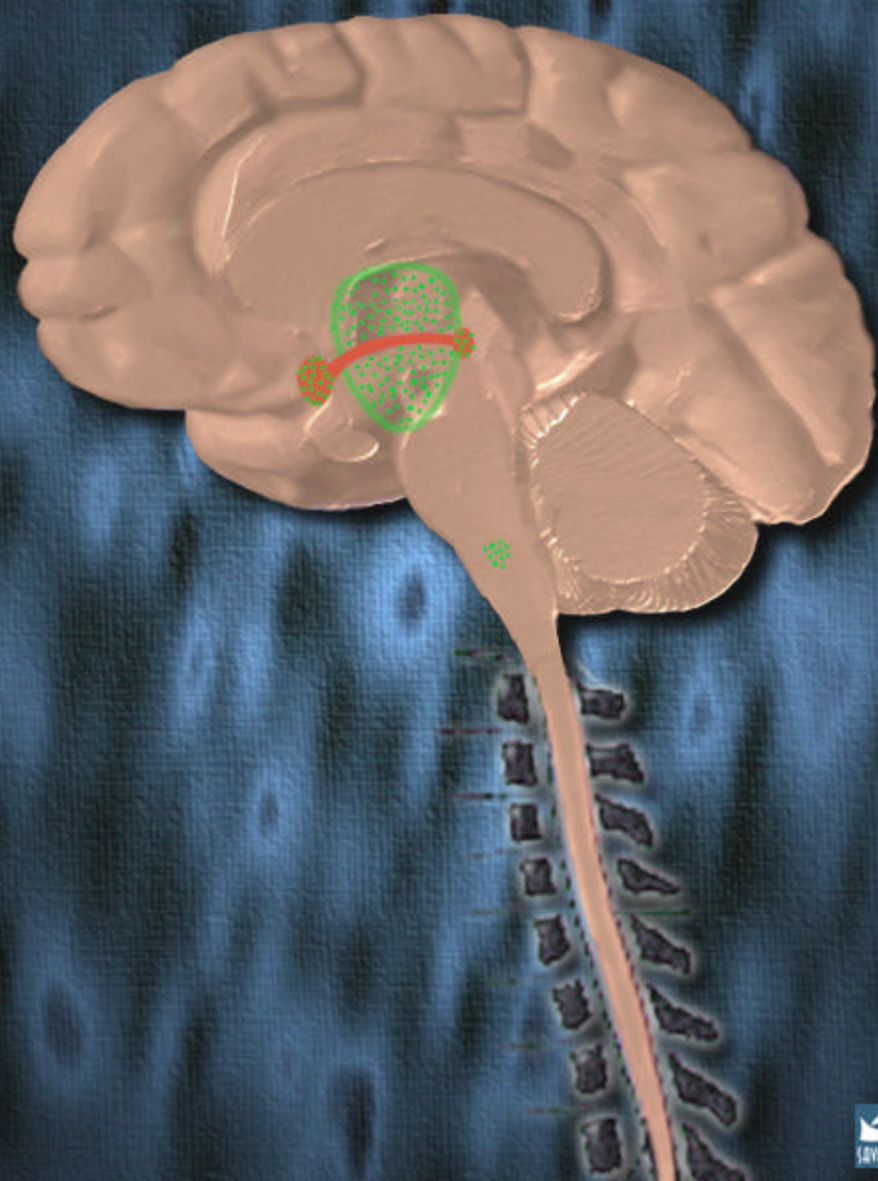


# Dependence

A state in which an organism functions normally only in the presence of a drug

- manifested as a physical disturbance when the drug is removed (withdrawal)



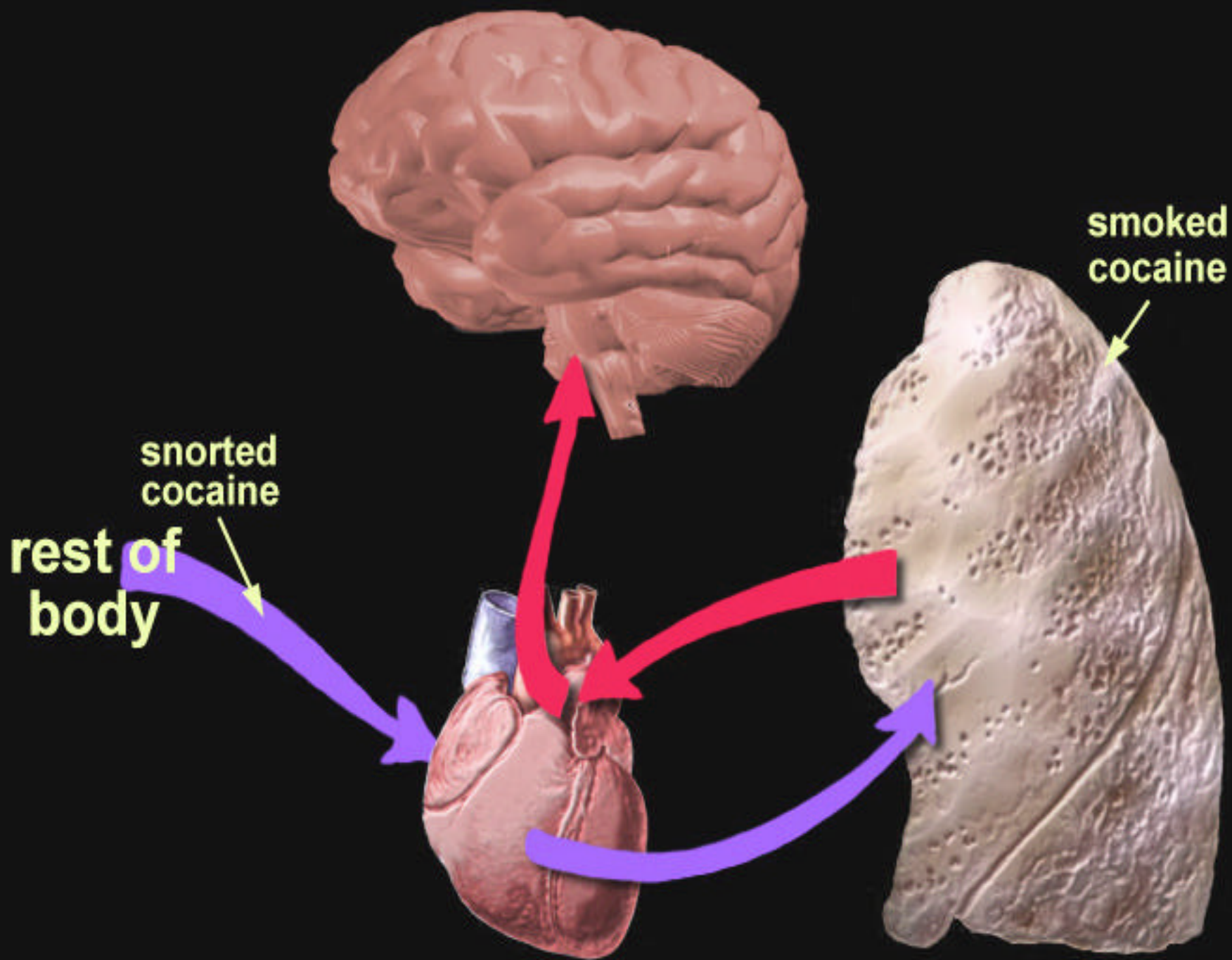


**addiction**

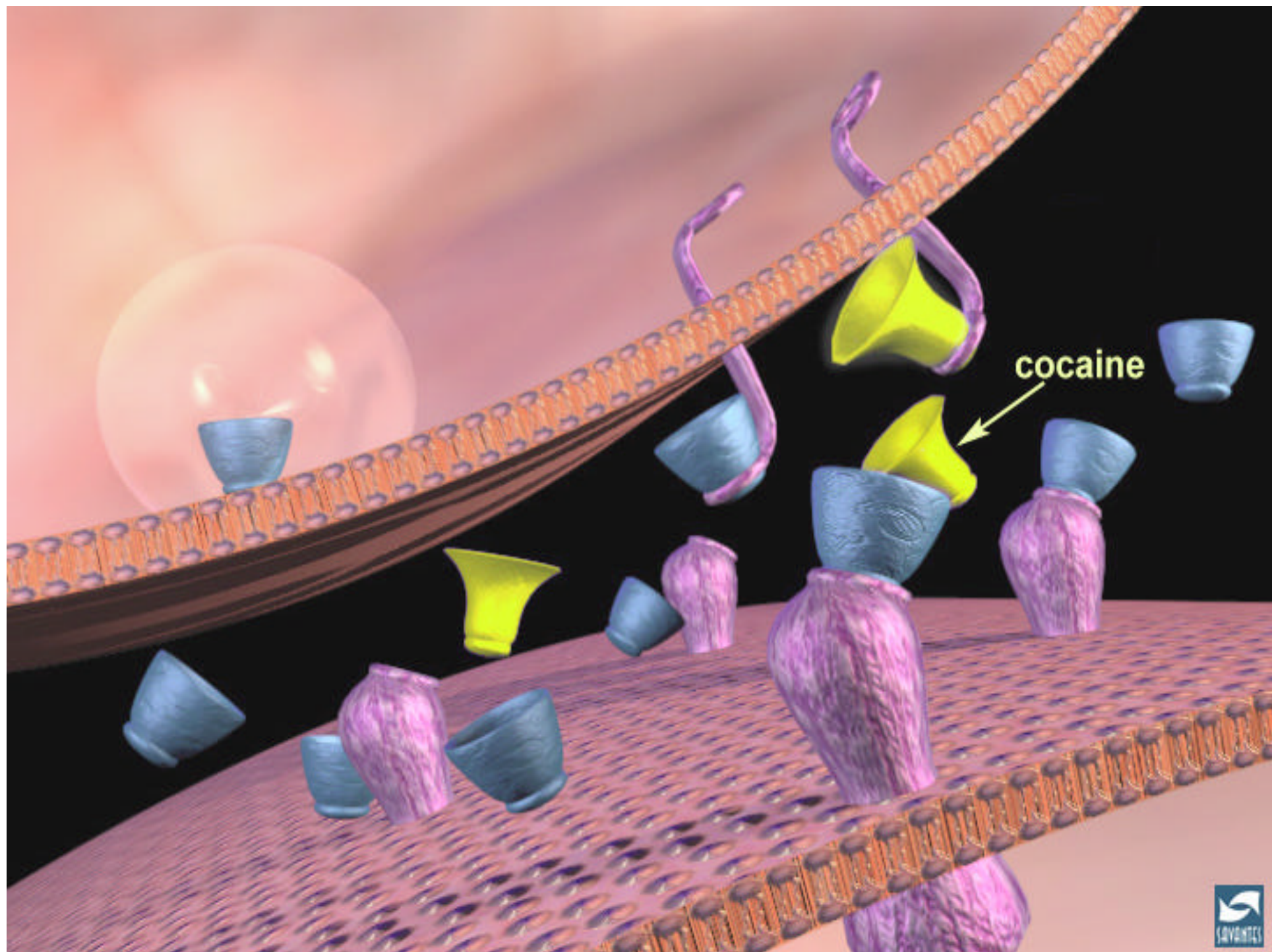
**dependence**



# The Action of Cocaine

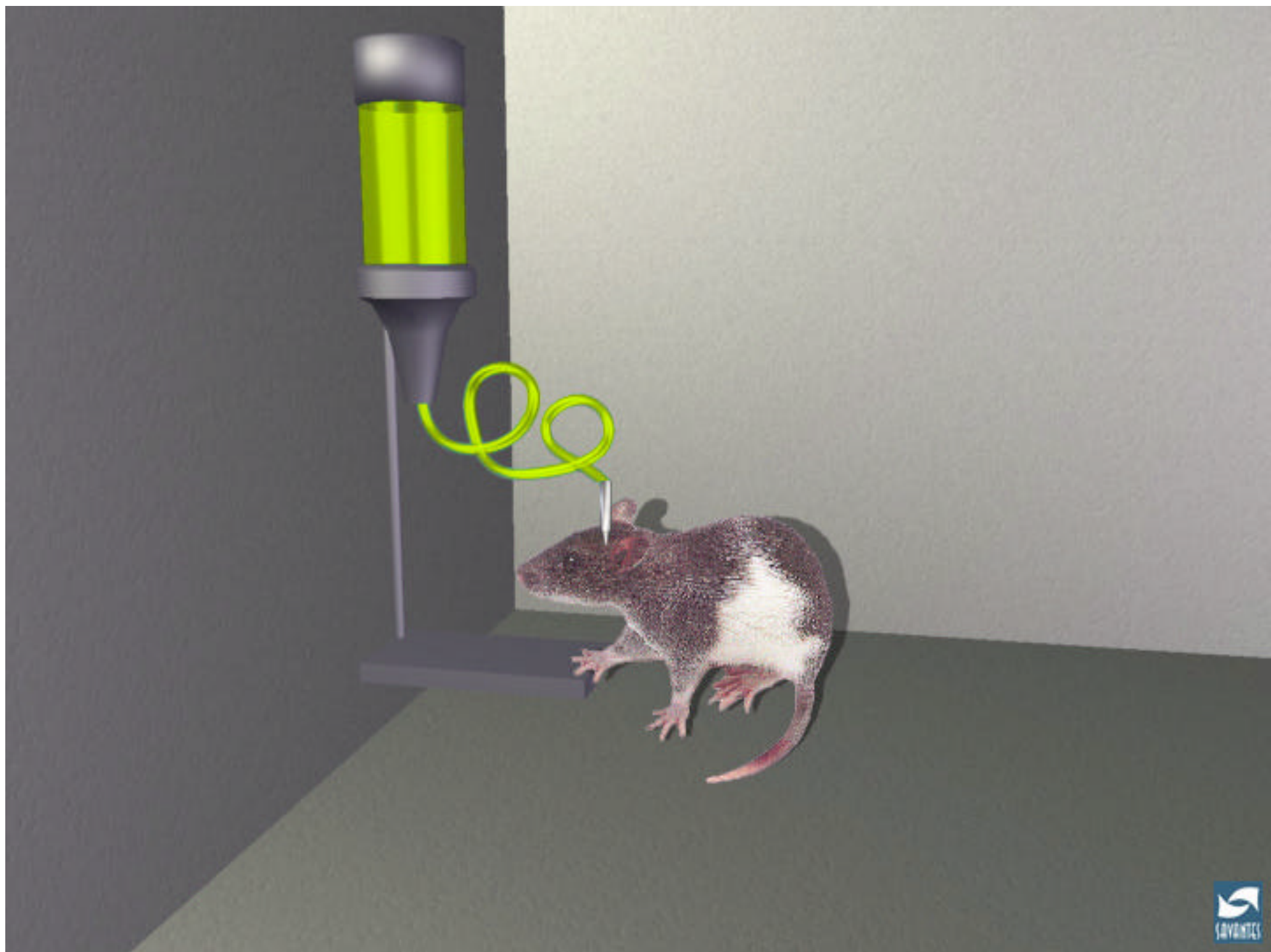








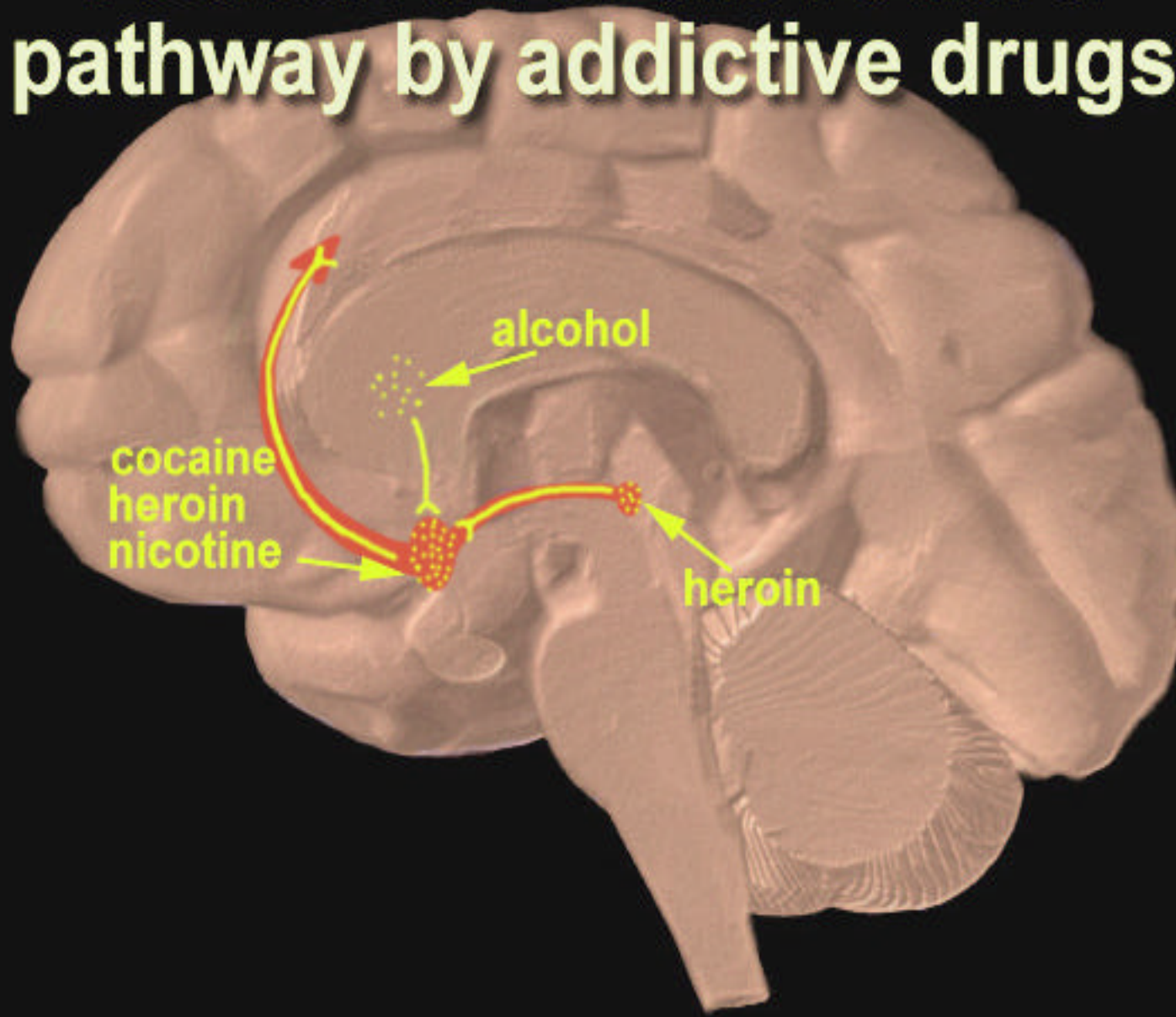




**Beer is proof that God loves us  
and wants us to be happy.**

**Benjamin Franklin**

# Activation of the reward pathway by addictive drugs



**WHY DO ADDICTED PEOPLE  
CONTINUE USING THESE  
SUBSTANCES DESPITE THE HARM?**

**Opium addiction is an  
insanity of the will.**

**Samuel T. Coleridge**

**poet, philosopher, opium addict**



**Sometimes when I reflect back on all the beer I drink I feel ashamed.**

**Then I look into the glass and think about the workers in the brewery and all of their hopes and dreams.**

**If I didn't drink this beer, they might be out of work and their dreams would be shattered.**

**Then I say to myself, "It is better that I drink this beer and let their dreams come true than be selfish and worry about my liver."**

**Jack Handy**

# WHY USE DESPITE HARM?

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- **ANIMAL STUDIES: SELF-ADMINISTRATION OF ELECTRICAL STIMULATION OR COCAINE LEADS TO LESS SOCIALIZATION, LESS SEX, LESS EATING**
- **RISK FACTOR: ABNORMAL FRONTAL LOBE EEG ACTIVITY**
- **DIFFERENT BRAIN CIRCUITS FOR HARM AVOIDANCE AND REWARD**
- **DISCONNECTION OF PREFRONTAL CORTEX**

**WHY RELAPSES?**

# Persistent Changes in Addicted Brain

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- CHRONIC AMPHETAMINE USE BLOCKS DOPAMINE SYNTHESIS FOR UP TO 1 YR
- AFTER FEW USE TRIALS, DOPAMINE RELEASE FOLLOWS CUE, BEFORE DRUG
- CUE-DRUG and CUE-STRESS PAIRING NEURONS SENSITIZED MONTHS TO 2 YEARS
- STRESS AND NEGATIVE EMOTIONS OFTEN CUE RELAPSE
- SUBSTANCE-INDUCED FRONTAL LOBE CHANGES LAST MONTHS, MAY EXPLAIN STRESS EFFECTS AND DEFICITS IN PLANNING



# Functions of Prefrontal Cortex

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- Inhibiting automatic, previously rewarded behaviors
- Shifting attention to new cues
- Learning new or modified motor behaviors after a new or related cue
- Inhibiting amygdala and stress response
- Reducing consumptive behavior after satiety

# Animal models of relapse

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- Reintroduction of drug after 3-12 months abstinence results in increased drug use
- Uncontrollable stress yields increased drug use once stressor is removed
- Place preference persists 3-12 mos.

# Cues for drinking or drug use

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- Alcohol, drugs and paraphernalia
- Sites of purchase/use
- Physical discomfort/illness
- Negative emotions after **stress**  
[sadness, anger, anxiety]



# Brain Changes in Cued Cocaine Craving

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- Amygdala [Stressful emotion]
- Anterior Cingulate [Arousal]
- Prefrontal Cortex

[Inhibiting, New Cue Response, Learn New Response]

S Lukas et al., 2000

# Medications that Decrease Cue-Induced Craving and Clinical Relapses

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- Nalmefene [Alcohol]
- Acamprosate [Alcohol]
- Naltrexone [Alcohol, Opioids]
- Methadone [Opioids]
- LAAM, buprenorphine [Opioids]

# Protective Factors

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## 1. Reduced environmental cues:

- 10% of heroin-addicted Vietnam vets remained addicted one year after military discharge
- Relapses among prisoners returning to home town very high for 6-12 months

## 2. Persistent support and professional job and addiction coping skills training, job support, psychiatric and medical services, etc. for 1-2 years

# Compliance, Relapse & Disorders

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<u>DISORDER/Tr'tment</u>	<u>COMPLIANCE (%)</u>	<u>% RETR'TED (12 mos)</u>
<b>Diabetes (Type I)</b>		<b>30-50</b>
Diet, foot care	< 30	
Medication	< 50	
<b>Hypertension (Rx-dependent)</b>		<b>50-60</b>
Diet	< 30	
Medication	< 30	
<b>Asthma (Adult)</b>		<b>60-80</b>
Medication	< 30	
<b>Addiction (Abstinence-Oriented Tx)</b>		<b>10-30</b>
Treatment Attendance	<40	
<b>Opioid Dependence (MMT)</b>	90	7

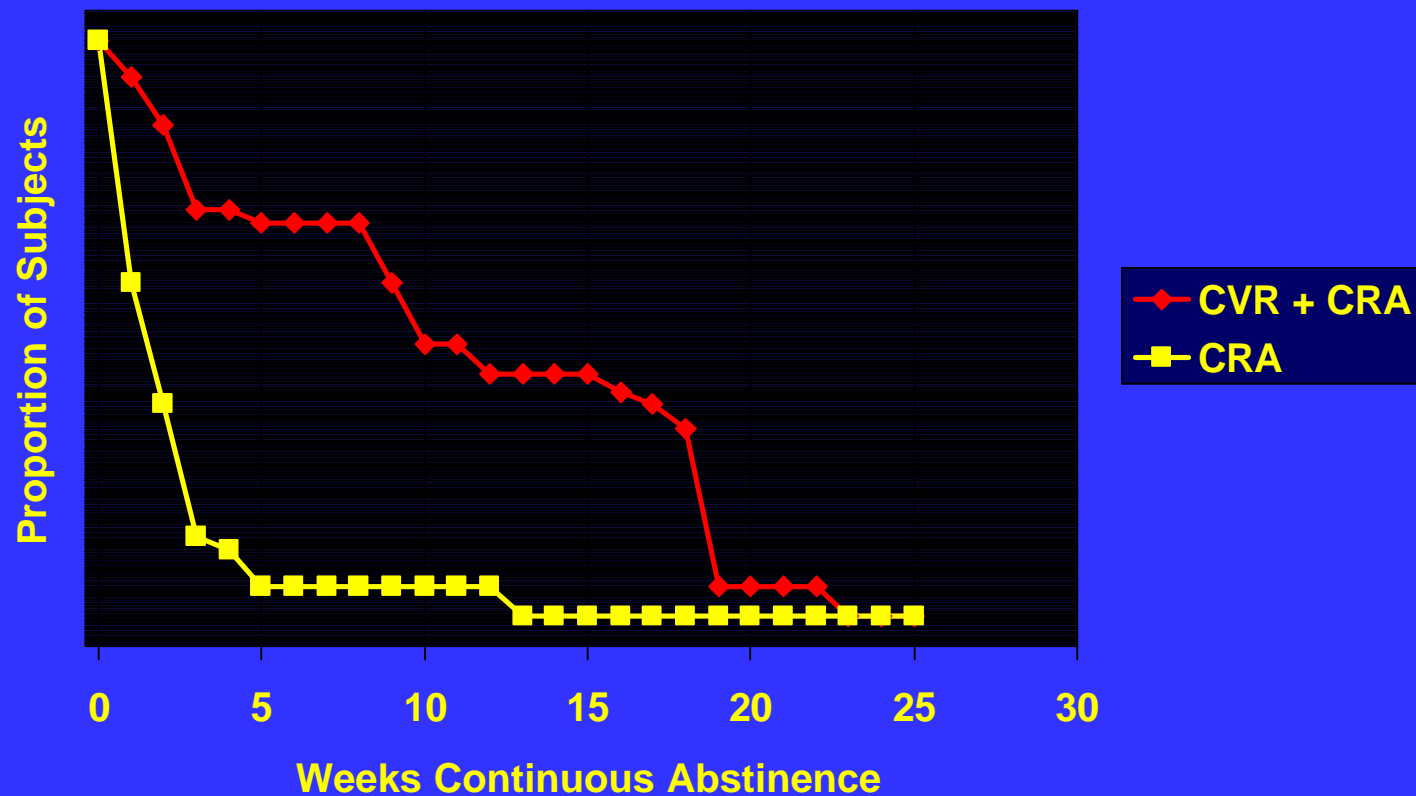


# COCAINE TREATMENT: Contingency Management

## ● Behavioral Approach

- Urine cocaine metabolite [8 day detection limit] measured weekly
- Points awarded contingent upon negative BE test: e.g., 5 points/week; 25 pt. bonus for 3 consecutive wks clean; exponential rise possible with value \$1K/26 wks
- Points redeemable for vouchered goods and/or services valued by addict and acceptable to counselor [examples: movie, meal, clothing, health club membership]

# Proportion of Subjects Maintaining Continuous Cocaine Abstinence in Outpatient Treatment



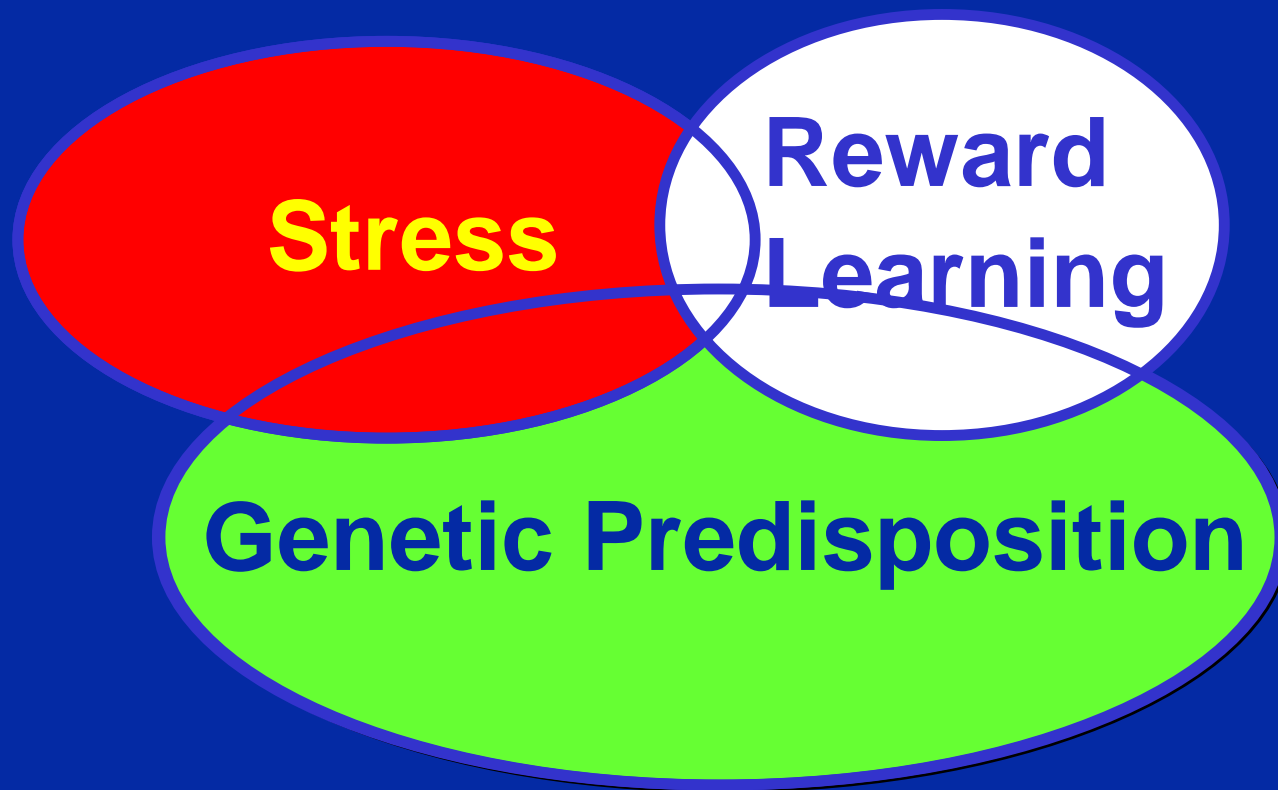
Higgins et al., 1993

# Contingency Management [CM] & Cocaine Dependence: Efficacy

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- **14 Studies: CM + CBT > CBT or no Tx**
- **2 studies: CM  $\geq$  equivalent random reward**
- **Nasal, IV, and Crack Users respond, as do Methadone Maintenance Treated cocaine addicts and schizophrenics**
- **Individual differences in reward threshold required to achieve and sustain abstinence**
- **Abstinence sustained 18 months after active treatment**

# Alcohol and Drug Dependence





# CONCLUSIONS

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1. **SUBSTANCE USE DISORDERS ARISE IN GREAT PART DUE TO HERITABLE VARIATIONS IN BRAIN ACTIVITY AT CRITICAL SITES.**
2. **ADDICTIVE SUBSTANCES' ACTIVITY AT THE NORMAL BRAIN REWARD CIRCUITS EXPLAINS MUCH OF COMPULSIVE USE AND ADDICTION.**
3. **RELAPSES IN ADDICTIVE DISORDERS LIKELY REFLECT PERSISTENT MEMORY CIRCUITS AND DEFICITS IN INHIBITION, PLANNING, & NEW LEARNING DUE TO ABNORMAL BRAIN ACTIVITY.**

**The Heart asks Pleasure--First--  
And then--Excuse from Pain--  
And then--those little Anodynes  
That deaden suffering--**

**And then--to go to sleep--  
And then--if it should be  
The will of its Inquisitor  
The privilege to die--**

**- Emily Dickenson, 1862**

# TREATMENT IMPLICATIONS

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1. Reduce use of long-term abstinence as a gold standard for assessing treatment outcomes
2. Decrease reliance on episodic care as cardinal aspect of rehabilitation treatment, focusing on maintenance and treatment of relapses.
3. Address considerable skill deficits of current substance abuse treatment providers in cognitive and behavioral treatment strategies, combination pharmacotherapy-psychotherapy treatments.

# TREATMENT IMPLICATIONS

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4. Increase availability of long-term supports such as halfway houses and low-intensity maintenance treatment for those doing well.
5. Reduce use of non-scientific education materials [e.g., PAWS, some commercial videotapes] regarding relapse process, using scientifically accurate information.
6. Decrease primary reliance on traditional abstinence-oriented, 12-step treatment for clients; use funds for reward-based treatments.



# TREATMENT IMPLICATIONS

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7. Increase use of assessment and treatment outcome measures that reflect severity of problems in multiple domains: drug/alcohol, psychiatric, medical, employment, legal, parental, family.
8. Assure adequate time for supervision.
9. Increase rewards for use of scientifically validated, effective treatment.
10. Use valid, multidimensional post-treatment assessments.